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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HANS BIGALKE and JURGEN FREVERT

Appeal 2010-000662
Application 10/018,373
Technology Center 1600

Decided: May 21, 2010

Before ERIC GRIMES, DEMETRA J. MILLS, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to methods for treating cosmetic conditions, dystonia, or nervous system disorders. The Patent Examiner rejected the claims on the ground of obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

STATEMENT OF THE CASE

Claims 11-18, which are all the pending claims, are on appeal. Claim 11 is representative and reads as follows:

> 11. A method of treating a human or animal with a cosmetic condition treatable with a botulinum neurotoxin, comprising administration, to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins, and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

The Examiner rejected the claims under 35 U.S.C. § 103(a) as follows:

- claims 11 and 14-15 in view of Keen[1] and Johnson;[2]
- claims 11-15 in view of Carruthers,[3] Heckmann,[4] and Johnson;
- claims 16-18 in view of Kessler[5] and Johnson; and
- claims 16-18 in view of Göschel[6] and Johnson.

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[1] Monte Keen et al., *Botulinum Toxin A for Hyperkinetic Facial Lines: Results of a Double-Blind, Placebo-Controlled Study*, 94 PLASTIC AND RECONSTRUCTIVE SURGERY 94-99 (1994).
[2] U.S. Patent No. 5,512,547, issued to Eric A. Johnson et al., Apr. 30, 1996.
[3] Alastair Carruthers et al., *Cosmetic Uses of Botulinum A Exotoxin, in* TISSUE AUGMENTATION IN CLINICAL PRACTICE: PROCEDURES AND TECHNIQUES 207-236 (AW Klein ed., Marcel Dekker New York 1998).
[4] Marc Heckmann, *Follow-up of Patients With Axillary Hyperhidrosis After Botulinum Toxin Injection*, 134 ARCH. DERMATOL. 1298-1299 (1998).
[5] Kirn R. Kessler et al., *Long-term treatment of cervical dystonia with botulinum toxin A: efficacy, safety, and antibody frequency*, 246 J. NEUROL. 265-274 (1999).

Dependent claims 12-15 and dependent claims 17-18 have not been argued separately and therefore stand or fall with independent claims 11 and 16, respectively. 37 C.F.R. § 41.37(c)(1)(vii).

OBVIOUSNESS

The Issue

The Examiner's position is that methods of administering *C. botulinum* toxin to treat the cosmetic conditions, dystonia, or nervous system disorders recited in the claims were known before Appellants' invention. The Examiner found that each of Keen (Ans. 3-4), Carruthers (*id.* at 7), Heckmann (*id.*), Kessler (*id.* at 10-11), and Göschel (*id.* at 13-14) taught administering botulinum toxin complex to a patient having one or more of the conditions recited in the claims. However, the Examiner found none of these references disclosed administering a neurotoxin "free of the complexing proteins which naturally form complexes with botulinum neurotoxins," to a patient that "already exhibits neutralizing antibodies against botulinum neurotoxin complexes." (*E.g.*, Ans. 4.)

The Examiner found that Johnson taught a purified botulinum toxin, free of the natural complexing proteins, and that Johnson suggested modifying the methods in the references. The Examiner repeated essentially the same finding regarding Johnson for each rejection, and concluded it would have been obvious to replace the complex used by Keen, Carruthers, Heckmann, Kessler, or Göschel, with Johnson's pure botulinum toxin

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[6] Hilke Göschel et al., *Botulinum A Toxin Therapy: Neutralizing and Nonneutralizing Antibodies—Therapeutic Consequences*, 147 EXPER. NEUROL. 96-102 (1997).

"because Johnson et al teach that the purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients." (E.g., Ans. 5.) According to the Examiner, it would have been expected that pure botulinum toxin "would be effective in treating patients that are nonresponders (hav[ing] neutralizing antibodies to botulinum toxin A complex) . . . ." (E.g., Ans. 5.)

Appellants "do[] not dispute that Johnson et al. teach a method of reducing antibody formation in a patient." (App. Br. 10.) However, Appellants contend that none of the rejections shows how the references teach or suggest administering Johnson's toxin to subjects "already exhibiting neutralizing antibodies." (*Id.*, emphasis deleted.) Appellants contend that Johnson teaches away from treating those subjects (*id.* at 11), and that the prior art provides neither a suggestion to treat those subjects nor an expectation of success (*id.* at 12). Repeating similar arguments for each rejection, Appellants argue that none of the rejections made a prima facie case for obviousness.

The issues with respect to each of the rejections are:

did the prior art teach away from the claimed methods; and

did the prior art provide an expectation of success for practicing the claimed methods?

Principles of Law

When determining whether a claim is obvious, an Examiner must make "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565,

1572 (Fed. Cir. 1995). "Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

Findings of Fact

1. We adopt the Examiner's findings concerning the Keen, Carruthers, Heckmann, and Kessler disclosures. (Ans. 3-4, 6-8 and 10-11.)

2. We adopt these findings the Examiner made concerning Johnson's disclosure:

> Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

(Ans. 4-5.)

3. We adopt these findings the Examiner made concerning Göschel's disclosure:

> Goschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages 98-99 and Table 3, page 101). Goschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A

complex (pages 98-99 and Table 3, page 101). Goschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goschel et al teach that based on these studies, second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102).

(Ans. 13-14.)

4. Göschel reported: "[a] very reliable *in vitro* neutralization test has been introduced to detect and quantify antibodies raised in patients during treatment with botulinum A toxin." (Göschel 100.)

5. Göschel's test "allowed discrimination between the sera that contained antibodies directed against the neurotoxin and those with antibodies against the stabilizing proteins." (*Id.* at 101.)

6. Göschel reported that the test was sensitive enough to "detect amounts of neutralizing antibodies so small as to be of no consequence for therapy." (*Id.*)

7. Göschel analyzed the antibodies in patients undergoing treatment and reported: "[a]ntibodies near the detection limit (0.0003 U/ml) were found in the sera of two patients who still responded to treatment (see Fig. 3, values marked with 'x')." (*Id.*)

8. Göschel's Figure 3 indicates "[t]he column marked 'x' represents the sera of two patients which contained traces of antibodies." (*Id.* at 99.)

9. Göschel disclosed: "[p]atients with titers higher than 0.001 U/ml, however, were resistant to therapeutic doses of botulinum A toxin." (*Id.* at 101.)

10. Göschel advised: "[k]nowledge of the antibody status can be helpful in showing the way to proceed in cases of unsatisfactory response to therapy." (*Id.*)

Analysis

A. The rejections over the combined teachings of Keen, Carruthers, Heckmann, or Kessler, with Johnson.

We cannot agree with the Examiner that at the time of the invention, a person of ordinary skill in the art would have reasonably expected success in treating a patient "already exhibit[ing] neutralizing antibodies against botulinum neurotoxin complexes." The Examiner asserted an expectation of success with the phrase "absent evidence to the contrary" (e.g., Ans. 5), but overlooked the evidence to the contrary in the prior art. *See, e.g.*, Johnson at col. 1, ll. 49-55 ("[t]his renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective"); or Kessler at 272 ("[s]econdary nonresponse . . . entails discontinuing treatment, depriving the patient of the most successful therapy available"). The rejection does not provide any evidence that a person of ordinary skill in the art would have reasonably expected a nonresponder to respond to Johnson's purified toxin.

We find that the cited prior art did not provide a reasonable expectation of success. We conclude that the rejections combining the teachings of Keen, Carruthers, Heckmann, or Kessler, with Johnson did not establish prima facie obviousness.

B. The rejection over Göschel and Johnson.

Both Göschel and Johnson taught that purified botulinum toxin, rather than toxin complex, should be administered in order to avoid an immune response against the non-toxin components of the complex. (FF 2 and 3.) Göschel also disclosed that neutralizing antibodies against the toxin itself may be present in a patient at such levels that they are of no consequence to therapy. (FF 6.) Göschel reported that two of the patients studied had low levels of neutralizing antibodies present but still responded to treatment. (FF 7.) According to Göschel, patients become nonresponders when the titer of neutralizing antibodies reaches 0.001 U/ml. (FF 9.) Given Göschel's disclosure that patients having low levels of neutralizing antibodies still respond to treatment, we conclude that it would have been obvious to use Johnson's purified toxin for further treatment in such patients, for the reasons that Göschel and Johnson teach.

We will affirm the rejection, but because we rely on facts in addition to those cited by the Examiner, we designate our decision as a new ground of rejection.

CONCLUSIONS

A. The rejections over the combined teachings of Keen, Carruthers, Heckmann, or Kessler, with Johnson.

The prior art did not provide a reasonable expectation of success for practicing the claimed methods. We conclude that the rejections did not establish prima facie obviousness.

B. The rejection over Göschel and Johnson.

The prior art provided a reasonable expectation of success for practicing the claimed methods. We conclude that the rejection established prima facie obviousness.

SUMMARY

We reverse the rejection of claims 11 and 14-15 under 35 U.S.C. § 103(a) in view of Keen and Johnson.

We reverse the rejection of claims 11-15 under 35 U.S.C. § 103(a) in view of Carruthers, Heckmann, and Johnson.

We reverse the rejection of claims 16-18 under 35 U.S.C. § 103(a) in view of Kessler and Johnson.

We affirm the rejection of claims 16-18 under 35 U.S.C. § 103(a) in view of Göschel and Johnson.

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .
>
> (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART, 37 C.F.R. § 41.50(b)

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